REMARKS

Claims 1-7 and 10-23 were pending in the application, and will remain pending following entry of the present amendment. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1-7 and 10-23 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-7 and 10-23 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. It is the Examiner's position that "[t]he claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> [t]he limitation 'a family of peptides that bind to the target' claimed in claims 1,22-23 has no clear support in the specification and the claims as originally filed. The specification discloses 'once the peptide library is formed, a target of interest is screened with the peptide library to identify one or more library members that bind to target...' The subject matter claimed in claims 1,22-23 broadens and/or alters the scope of the invention as originally disclosed in the specification.

Applicants refer the Examiner to the remarks submitted in their amendment of December 3, 2004, regarding support as it exists in the specification for the term "family of peptides that bind to the target." As both described therein and in greater detail below, the term "family of peptides" is an art-recognized term that is supported in the specification at least at page 12, lines 24-27 (in reference to the "G-protein coupled, seven transmembrane receptor ***superfamily***"). Thus, inclusion of the term "family of peptides that bind to the target" in the present claims does not constitute an incorporation of new matter. Applicants respectfully remind the Examiner that for a claim to satisfy the written description requirement, the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*). As phrased by the court in

Fujikawa v. Wattanasin, 93 F.3d 1559, 39 USPQ2d 1895 (Fed. Cir. 1996), "*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of 35 U.S.C. § 112. Instead, the disclosure need only reasonable convey to persons skilled in the art that the inventor had possession of the subject matter in question." *Id.* at 1570. In view of the aforementioned considerations, Applicants' use of the term "family of peptides that bind to the target" is both art-recognized and adequately supported by the specification and, therefore, does not constitute an addition of new matter. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 1-7 and 10-23 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-7 and 10-23 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. It is the Examiner's position that "[t]he claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> [t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568,43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.
>
> Although directed to DNA ***compounds***, this holding would be deemed to be applicable to any compound; which requires a representative sample of ***compounds*** and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s). (***Emphasis added***).

Applicants respectfully traverse the foregoing rejection for the following reasons. As an initial matter, Applicants respectfully submit that the Examiner's rejection appears to be focused on a perceived lack of description of specific compounds in the present specification when, in fact, the claimed invention is directed to ***screening methods*** and not the compounds that are identified by these screening methods.

Moreover, Applicants submit that the specification contains ample description of the claimed screening assays. Indeed, while not required for patentability, Applicants have put to practice the claimed methods and Applicants' specification contains working examples describing the claimed methods. Specifically, within the Examples section of the present specification, Applicants have described the methods of the invention used to identify compounds that bind to the luteinizing hormone releasing hormone receptor (LHRH-R), detailing the steps of: (a) constructing a first library; (b) screening the first library; (c) generating a peptide motif; (d) constructing a second library; (e) screening the second library; and (f) identifying the structure or structures of compound(s) that binds to the target, in sufficient detail that one of ordinary skill in the art would understand Applicants to be in possession of the claimed invention at the time of filing.

Applicants additionally refer the Examiner to the sections spanning page 4, line 6 through page 7, line 10 and page 12, line 30 through page 14, line 20 of the specification where Applicants exemplify the production of the first (peptidic) library and describe well known methods for generating this library. Applicants also refer the Examiner to the sections from page 8, line 30 through page 10, line 27 and page 15, line 7 through page 16, line 2 of the specification where Applicants exemplify the production of the second (non-peptidic) library and describe well-known methods for generating this library.

In view of the above, one of ordinary skill in the art would understand that Applicants were in possession of the claimed methods of the instant invention at the time of filing. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 1-7 and 10-23 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-7 and 10-23 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention." Specifically, the Examiner is of the opinion that

> [c]laims 1-7,10-23 are vague and indefinite by reciting 'non-peptide', which are selected from peptide derivatives or analogues or peptidomimetics, wherein a single amino acid or few specific amino acids are replaced by synthetic or non-natural amino acids. However, the specification has not disclosed how many amino acids replaced and which amino acids were replaced, and further the term 'non-peptide' may read on small organic molecules which were not the peptide derivatives or peptide analogues or contain the non-natural amino acids as in applicants disclosure. Thus, the metes and bounds of the term non-peptide' is not clear.
>
> The instant claims recite 'family of peptides', which is vague and indefinite. The term 'family of peptides' would refer to a group of peptides, which share similar properties, such as epitopes or binding affinity or mimic a specific property. However, it is not clear which peptides are considered as family of peptides.

Applicants traverse this rejection on the grounds that the terms "non-peptide" and "family of peptides" are clear and definite as described in the present specification, presented in the instant claims and as known to one of ordinary skill in the art. Specifically, the present specification has defined the term "non-peptide compounds" "to include compounds comprising at least one molecule other than a natural amino acid residue, wherein the structures of the compounds cannot be determined by standard sequencing methodologies but rather must be determined by more complex chemical strategies, such as mass spectrometric methods." Furthermore, the presently pending claims specify that the "non-peptide compounds" are peptide analogues, peptidomimetics or peptide derivatives. The terms "peptide analogues", "peptidomimetics", and "peptide derivatives" are each art-recognized and are also expressly defined in the present specification, at least in the section from page 8, line 36 through page 9, line 11. In view of the foregoing express definitions in Applicants' specification (which are consistent with the art recognized and accepted use of these terms), one of skill in the art would find the term "non-peptide" to be clear and definite. Therefore, the Examiner's rejection is improper.

The Examiner's rejection of the term "family of peptides" as indefinite is also improper. Applicants again refer the Examiner to the remarks submitted in their amendment of December 3, 2004. As described therein, the term "family of peptides" is an art-recognized term that is described in the specification at least at page 12, lines 24-27 (in reference to the "G-protein coupled, seven transmembrane receptor ***superfamily***"). Further, Applicants submit that the Examiner has, in fact, admitted that this term is clear and definite by providing in the present Office Action the art-recognized definition of the term "family of peptides." Specifically, the Examiner states that "[t]he term 'family of peptides' would refer to a group of peptides, which share similar properties, such as epitopes or binding affinity or mimic a specific property." As described in the present specification, the shared property of the "family of peptides" featured in the instant invention is that of binding to a common target. In view of the foregoing, it is evident that one of ordinary skill in the art would find the term "family of peptides" to be clear and definite. The Examiner's rejection of the term "family of peptides" is, therefore, also improper. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 1-7 and 10-23 Under 35 U.S.C. §101

The Examiner has rejected claims 1-7 and 10-23 under 35 U.S.C. §101, asserting that the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility. In particular, the Examiner is of the opinion that

> [t]he non-peptide compounds identified by the instant claimed method are not supported by a specific, substantial, asserted utility and do not, without further research and experimentation, provide an immediate benefit to the public. The non-peptide compounds identified may bind to LHRH-R, however the specification has not taught the substantial utility of these compounds. The specification discloses that the non-peptides which bind to LHRH-R are identified, however has not disclosed the binding affinity or dissociation constant of the non-peptides with the LHRH-R, or assay in which the binding of the non-peptides with the LHRH-R were tested. Rather, the identified non-peptide compounds require further research to identify whether the compounds are useful in therapy or diagnosis. The specification discloses that 'to optimize the benefits of both

> peptide based and chemically based libraries, the methods of the invention involve utilizing information obtained from screening a target with a first library comprising a multiplicity of peptides in the design of a second library comprising multiplicity of non-peptide compounds.' The specification discloses that the methods provide diversity and ease of deconvolution of traditional peptide library. The specification has not disclosed the high affinity compounds identified or the use of these high affinity compounds. Thus, any benefit to the public (to one of ordinary skill in the art) is speculative of the claimed method. There is no basis in the specification upon which to conclude that *any* of the non-peptides encompassed by the second library are, or will turn out to be, biologically active (therapeutic or diagnostic) after testing. Thus, the biomedical research contemplated by applicants is to take place at some future time, only when the properties of the claimed compounds have been elucidated by the experimental methods (screening assays) to which the specification alludes. Absent a disclosure of those properties, the asserted utility lacks specificity. Note, because the claimed invention is not supported by a specific asserted utility for the reasons just set forth, credibility cannot be assessed.

Applicants respectfully traverse this rejection as it pertains to the pending claims for at least the following reasons. As an initial matter, Applicants wish to remind the Examiner that the claimed invention is directed to methods for identifying a non-peptide compound that binds to a target. The claimed invention is not directed to the compounds that are identified by the claimed methods and thus, the Examiner's rejection which is based on the assertion that "[t]he non-peptide compounds identified by the instant claimed method are not supported by a specific, substantial, asserted utility[,]" is irrelevant to the pending claims. The proper inquiry should be whether the claimed methods have a well-established utility. For the reasons set forth below, Applicants respectfully submit that the claimed methods do have a well-established utility.

As indicated by the M.P.E.P (see § 2107),

> [a]n invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Applicants respectfully submit that a ***well-established*** utility for the claimed invention is immediately apparent from Applicants' specification and the knowledge in the art at the time of Applicants' invention, and that this asserted utility is ***credible, specific and substantial.*** The present invention is directed to compound-enrichment/identification screening assays that have a

well-established utility. The instant specification discloses that the claimed methods identify at least one non-peptide compound that binds to a target molecule (the target molecule may be any molecule to which identification of non-peptide compounds that bind to the target molecule might be desired, including, e.g., therapeutic target molecules). Such compound screening assays have a well-established utility in the field of drug discovery, providing processes by which test pools of compounds may be enriched for desired properties (e.g., binding to therapeutic targets). ***Indeed, an entire industry has been built upon the market value ascribed to pharmaceutical compound screening assays.*** The Examiner need look no further than the U.S. Patent database for indication of the well-established utility of such screening assays. For example, Applicants wish to direct the Examiner's attention to the claims that have issued in U.S. Patent No. 6,455,263 (Donald Payan, "Small molecule library screening using FACS"), U.S. Patent No. 6,905,818 (Erich Wanker *et al.*, "Method for the identification and characterization of interacting molecules by automated interaction mating"), and U.S. Patent No. 6,737,240 (Ziang Xu *et al.*, "Methods of screening for a multi-drug resistance conferring peptide").

Applicants further respectfully submit that

> the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. §2164.07.

In view of the foregoing, Applicants respectfully submit that that the presently claimed methods have a ***well-established utility*** that would have been readily apparent to one of skill in the art at the time of the invention.

Applicants further submit that the uses of the claimed methods are ***specific, substantial and credible.*** As discussed above, the instant specification discloses methods of identifying a non-peptide compound capable of binding to a target molecule. It was well-known in the art as of the filing date of the instant application that methods of enriching for compounds that bind to, *e.g.*, a therapeutic target have utility in the drug discovery process. As described in the present

specification, the methods of the present invention commence with preparation of a first library comprising a multiplicity of peptides. Such a library may even include a library of random peptides, the vast majority of which would be incapable of binding to a desired target molecule, and therefore of minimal value in the drug discovery process. In contrast, the non-peptide compounds identified *via* practice of the methods of the present invention are each capable of binding to a desired target molecule, rendering this output group of compounds of much greater value in the drug discovery process, if only because of the tremendous fold-enrichment in desirable target-binding compounds that may be achieved *via* practice of the methods of the instant invention.

The specific utility of the present invention is further supported by the results obtained when the claimed invention is put to practice. For example, Applicants direct the Examiner's attention to PCT Publication WO97/22617 (previously submitted), which is a published international application corresponding to the present application. Example 2, at pages 19-26 of this PCT application, presents data that were obtained *via* performance of the methods of the instant invention, that demonstrates that relative to the unselected library, the potency (in terms of binding affinity for a substrate) of the selected population of non-peptide compounds (selected according to the claimed methods) was increased by approximately 1000-fold (see in particular page 24, lines 30-32). This dramatic increase in the potency of a peptide population, achieved *via* practice of the instant invention, underscores the ***specific*** utility of the instant invention.

Moreover, based on the knowledge of one of ordinary skill in the art regarding the drug discovery process, Applicants respectfully submit that the use of the claimed methods is also ***substantial and credible.*** Specifically, identification of one or more non-peptide compounds, each of which binds to a chosen target molecule, is a desirable outcome based upon a need in the art, and the disclosed uses of the methods of the instant invention are a substantial and a "real world" use.

In view of the teachings in Applicants' specification and the general knowledge in the art at the time of the filing of the application, it is evident that the ordinarily skilled artisan would find the utility of the claimed methods to be ***well-established as well as specific, substantial and credible.*** Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 1-3, 5-7, 10-16 and 21-23 Under 35 U.S.C. §103(a) Over Lam et al. and Gallop et al.

The Examiner has rejected claims 1-3, 5-7, 10-16, 21-23 under 35 U.S.C. 103(a) as being unpatentable over Lam *et al.* (U.S. Patent 5,650,489) and Gallop *et al.* (Journal of Medicinal Chemistry. Vol. 37, Number 9, April 1994, pages 1233-1251). The Examiner relies on Lam *et al.* for teaching

> a library of bio-oligomers of defined size and known composition, in which the library contains all of the possible sequences of the bio-oligomers, and methods of synthesis of the library, and the bio-oligomers are peptides. And the reference methods include methods to identify bio-oligomer from the library that demonstrate the desired characteristics, such as binding (refers to the instant claim steps a-b) (i.e., see the abstract). The reference teaches that the method may be used for synthesis of random peptides as well as for synthesis of a peptide library that comprise pre-determined sequences (i.e., see column 10). The reference teaches that the method includes steps of generating a random library of peptides; contacting the library with target (acceptor); and isolating the library members which exhibit binding to the target; and sequencing the identified library members (i.e., see column 5).
>
> Lam et al teach that the peptide libraries comprising D-amino acids, peptidomimetics, peptidomimetic bonds, and non-classical amino acids (i.e., see column 11-13). The reference teaches that the structure of the peptides comprising non-classical peptides is determined by mass spectral analysis (i.e., see column 13). The reference teaches the methods for modification or derivatization of the peptides in the library (i.e., see column 13,14). Lam et al teach that the peptides comprising D-amino acids (non-peptides of the instant claims) will be resistant to L-amino acid-specific proteases in vivo. And the reference teaches that the modified peptide bond compounds (non-peptides) would be resistant to peptide bond hydrolysis, and such libraries would provide ligands with unique function and activity, such as extended half-lives in vivo due to resistance to metabolic breakdown or protease activity (i.e., see column 11)
>
> The reference teaches that the bio-oligomers of interest discovered during an initial screening need not be final ligands. In fact, it is preferable to synthesize a second library based on common sequences (peptide motif) of the ligands selected during the first screening,. In this way, one may be able to identify ligands of higher activity, (i.e., see column 16, last paragraph bridging column 17).

The Examiner admits that

> ***Lam et al do not teach that the second library which is based on the ligand identified from the initial (first) library is non-peptide.*** However, Lam et al teach the use of D-amino acids or non-natural amino acids in the synthesis of the peptide libraries. A person skilled in the art would have been motivated to use the methods of synthesis of peptides and non-peptides taught by Lam et al to synthesize a second library based on the ligand

selected from the first library, and identify the non-peptide compound which binds to the target, and determine the structure of the compound, because Lam et al teach that the method would allow to identify higher affinity or active compounds. And it would have been obvious to one skilled in the art at the time the invention was made to make multiple (or a third) library based on the non-peptide selected and screen the library for active compounds, such more diverse or higher affinity compounds would be identified. (***Emphasis added***).

The Examiner further relies upon Gallop *et al.* for

review[ing] the applications of combinatorial technologies to Drug Discovery and peptide combinatorial libraries. Gallop et al teach the building block strategy , and the number of possible different individual compounds, N, prepared depends on number of building blocks used in each step, b, and number of synthetic steps in the reaction scheme, x, Gallop et al teach the phage display peptide libraries and methods of screening for active peptides. Gallop et al teach phage display libraries of 10^7 to 10^8 recombinants. The reference teaches antibody library synthesis, and method of screening with an antigen, and in vitro affinity improvements of the large number of selected clones. The in-vitro affinity improvement is accomplished by continuing selection of the pool of antibodies, or by introducing sequence variation into the enriched antibody pool and reapplying selection (see right column in page 1236). Further the article includes combinatorial libraries using multipin synthesis, and mimotope strategy. Peptide mixtures (libraries) were synthesized using the 20 common L-amino acids, and screened for antibody binding, and the identified sequence then provides a basis for a further round of synthesis, in which both L- and D- amino acids, non- or other amino acids are used.

Thus, it was well known at the time the invention was filed to use the ligands identified in the first library as basis to synthesize a second library with non-natural amino acids and screen for improved activity ligands.

Thus a person skilled in the art would have been motivated to use the ligands (peptides) identified in the first library as basis for synthesis of non-peptide libraries because the non-peptide compounds would be useful as Pharmaceuticals or in therapy since the non-peptide compounds are resistant to proteolysis and have better half-lives in vivo.

<u>The Examiner has Failed to Provide the Necessary Motivation to Impel One of Ordinary Skill in the Art to Make Applicants' Invention</u>

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references renders the claimed invention obvious to the ordinarily skilled

artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

Claims 1-3, 5-7, 10-16, 21-23 are directed to methods for identifying a non-peptide compound that binds to a target. The method involves forming a first library ***comprising a multiplicity of peptides***; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby ***generating a peptide motif***; forming a second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, since the cited references alone or in combination, fail to teach or suggest the claimed invention and further fail to provide the necessary motivation or expectation of success for the ordinarily skilled artisan to identify a non-peptide compound that binds to a target by forming a first library ***comprising a multiplicity of peptides***; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby ***generating a peptide motif***; forming a second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, as required by Applicants' claims.

First, the primary reference relied on by the Examiner, namely, Lam *et al.*, teaches generation and usage of "a library of bio-oligomers of defined size and known composition, ***in which the library contains all of the possible sequences of the bio-oligomers*** . . . [t]he bio-oligomers of the library may be peptides, nucleic acids, or a combination of the foregoing". (Abstract of U.S. Patent 5,650,489). Lam *et al.* do not teach or suggest the claimed methods which require forming a first library ***comprising a multiplicity of peptides***; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby ***generating a peptide motif***; forming a second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target. Indeed, the Examiner has admitted that Lam *et al.* do not teach or suggest generating a second non-

peptidic library which is designed based on the peptide motif generated based on the screening of the first library (see above).

Moreover, the secondary reference of Gallop *et al.* does not make up for the deficiencies of the primary reference. Specifically, Gallop *et al.* review art-recognized methods for synthesis and use of peptide combinatorial libraries, with reference to affinity maturation techniques and recognition that libraries of variants may be designed based on lead peptides, using the "building block" strategy as cited by the Examiner. However, Gallop *et al.* does not teach or suggest methods for forming a first library ***comprising a multiplicity of peptides***; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby ***generating a peptide motif***; forming a second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, as required by Applicants' claims.

Furthermore, it is Applicants' position that the teachings of the cited references relied upon by the Examiner to combine the references are legally insufficient to provide the requisite motivation. With regard to the necessary legal standard, Applicants refer the Examiner to *Arkie Lures v. Larew Tackle*, 119 F.3d. 953 (Fed. Cir. 1997). In *Arkie Lures*, the Larew invention was directed to a "salt-impregnated fishing lure." In that case, the CAFC overturned the district court's finding of obviousness. The CAFC agreed that "[t]he use of salty bait to catch fish was known, [and] plastisol lures were known." *Id* at page 956. However, the CAFC found that although the literature on "fishing lures is apparently quite extensive, but despite the long use of salty lures and plastic lures, no reference was cited that showed or suggested this combination." The CAFC continued that "[t]he evidence showed the complexity of the plastic fishing lure art. Those in the field of the invention viewed Larew's invention not as a simple concept of adding

salty taste to a known lure, but as a complex combination requiring experience of fishing and fishing lures and the technology of plastics." Id at page 957.

The court further stated that:

> No prior art showed or suggested the combination of a plastisol lure with salt, although the prior art was extensive as to the separate elements, and suggested including organic attractants in plastic lures. . . . The question is not whether salt "could be used," as the district court concluded, but whether it was obvious to do so in light of all the relevant factors. . . ***.It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements***. Indeed, the years of use of salty bait and of plastic lures, without combining their properties, weighs on the side of unobviousness of the combination. (***Emphasis added***).

Id at pages 957 and 958.

Similar to the situation in the *Arkie Lures* case, the teachings of the cited references alone or in combination are ***insufficient*** to establish the obviousness of the claimed invention absent some teaching or suggestion in the art to combine and modify the teachings of those references to arrive at the claimed invention. The Examiner argues that the motivation would arise from the teachings of Lam *et al.* to generate and use a library of bio-oligomers of defined size and known composition, in which the library contains all of the possible sequences of the bio-oligomers and the teachings of Gallop *et al.* to perform art-recognized synthesis of peptide combinatorial libraries, including affinity maturation techniques, for development non-peptide libraries. These general statements directed to certain elements of the claimed invention fail to provide a specific teaching or suggestion which would motivate the ordinarily skilled artisan to make a ***non-peptidic secondary library possessing ligand-binding attributes, wherein the secondary library is based on a peptide motif that also possesses ligand-binding attributes and is identified by screening of a primary peptide library***, as required by Applicants' claims. Moreover, it is Applicant's position that the motivation relied upon by the Examiner, which is not based on explicit suggestions within the cited references, but rather on what the Examiner

argues that one of ordinary skill in the art would have known, is legally insufficient to establish the requisite suggestion to combine references.

In further support of their position, Applicants point to the recent CAFC decision in *In re Rouffet* (*In re Rouffet*, Lexis 16414 (Fed. Cir. 1998)). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The Examiner rejected Rouffet's claims as unpatentable over U.S. patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Staellite Communications System" (Ruddy).

In *Rouffet* the Court of Appeals found that:

> ***[b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight.*** This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See In re Gorman, 933 F.2d. 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy. (*Emphasis added*).

In re Rouffet at [*17].

Similarly, it is Applicants' position that since the Examiner has selected prior art references which teach synthesis and use of a library of bio-oligomers of defined size and known composition, in which the library contains all of the possible sequences of the bio-oligomers (Lam et al.) and methods for synthesis and use of peptide combinatorial libraries (Gallop et al.) , and has not pointed to any teaching or suggestion in the art that would impel the ordinarily skilled artisan to modify the cited art to arrive at Applicants' invention, it is Applicants' position that the Examiner has used Applicants' invention as a blueprint to

combine the references. The CAFC has ruled that "[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional purpose in enacting Title 35.'" *Smith Kline Diagnostics*, 859 F.2d. at 886-887 (citing *Panduit Corp v. Dennison Mfg. Co.*, 810 F.2d. 1561, 1577 (Fed. Cir. 1987)) (citations omitted).

Additional support of the position that the claimed invention is unobvious is found in *In re Vaeck* (*In re Vaeck* 947 F.2d 488. (Fed. Cir. 1991)) where the CAFC upheld the nonobviousness rejections of a biotechnology invention. In *Vaeck* the invention was drawn to "a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the Bacillus genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing the Bacillus gene in a host cyanobacterium, so as to produce the desired insecticidal protein (footnote omitted)." *Id* at page 490. The prior art (a total of eleven references) was applied in various combinations against the claims. The primary reference (Dzelzkalns) taught the expression of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT) in cyanobacteria. The secondary references taught, *inter alia,* "expression of genes encoding certain *Bacillus* insecticidal proteins" in other host cells; "the initiation specificities *in vitro* of DNA-dependent RNA polymerases purified from two different species of cyanobacteria (footnote omitted);" and "a host-vector systems for gene cloning in the cyanobacterium." *Id* at page 491. The Examiner's position was that:

> it would have been obvious to one of ordinary skill in the art to substitute the Bacillus genes [which had been expressed in heterologous hosts in the teachings of the prior art] for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the Bacillus genes in the transformed cyanobacteria. The Examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes.

Id at page 492.

The CAFC disagreed with the Examiner's position and found that the teachings of the prior art cited in *Vaeck* were not sufficient to support the interchangeability of bacteria and cyanobacteria as host organisms for the expression of heterologous insecticidal proteins. The court stated that "there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding Bacillus insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria." *Id* at page 493. The court further stated that while the prior art disclosed "expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts. . . . [w]hile it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. *Id* at pages 493 and 494.

The CAFC contrasted its findings in *In re Vaeck* with those in *In re O'Farrell* stating "[i]n contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art." In *O'Farrell* the invention was directed to a "method for producing a predetermined protein in a stable form in a transformed host species of bacteria." *In re O'Farrell* 853 F.2d 894. 1988. 7 U.S.P.Q. 2d (BNA) 1673. The prior art (Polisky) taught a previous attempt to "control the expression of cloned heterologous genes inserted into bacteria." *Id* at page 899. The prior art differed from the claim at issue, however, because it taught a method of expressing "a segment of DNA from a frog that coded for ribosomal RNA," which is normally not translated into protein. Although ribosomal RNA is not normally translated into protein, the court found that in the prior art publication by Polisky the authors were "obviously interested in using their approach to make heterologous proteins in bacteria." *Id* at page 900. The CAFC referred to the Polisky paper which stated:

> In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of Xenopus [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Id at page 900 (quoting from Polisky *et al.* at page 4904).

The court stated that "[t]he authors of the Polisky paper ***explicitly pointed out*** that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a 'fused protein' consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain." *Id* at page 901. The court also referred to a passage in the Polisky reference, where the authors stated that "[i]f an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Id at page 901 (quoting from Polisky *et al.*). The court upheld the PTO decision that the claims in *O'Farrell* were obvious over Polisky because:

> ***virtually everything in the claims was present in the prior art.*** . . . The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. . . .Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, 'a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide.' ***Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.*** (Emphasis added).

Id at 901.

It is Applicants' position that, as in *In re Vaeck*, there is no teaching, neither explicit nor implicit, in any of the references cited by the Examiner, which would have impelled one of ordinary skill in the art to make the instantly claimed invention. ***The art cited by the Examiner***

is directed to individual elements of Applicants' invention, and not to the invention as a whole (Lam *et al.* teach methods for synthesis and use of a library of bio-oligomers of defined size and known composition, in which the library contains all of the possible sequences of the bio-oligomers and Gallop *et al.* reviews art-recognized approaches to synthesis of peptide combinatorial libraries, including reference to affinity maturation techniques and design of variant libraries based on a lead compound). Given the standard for obviousness set forth by the CAFC, it is Applicants' position that the Examiner has improperly relied on hindsight obtained from Applicants' invention in making the combination of references cited.

Applicants' Unexpected Results Further Demonstrate That the Examiner Has Failed to Establish a *Prima Facie* Case of Obviousness

Even assuming *arguendo* that a *prima facie* case of obviousness were established by the Examiner, which Applicants dispute, the non-obviousness of the invention is apparent from the results achieved when the invention is put into practice. "One way for an Applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results', *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." In re Soni, 54 F.23d 746, 34 USPQ2d 1684 (Fed. Cir. 1995).

Use of the claimed invention as described in the specification, allows for the identification of compounds that have unexpectedly improved binding properties. Applicants refer the Examiner to PCT Publication WO97/22617 (submitted as Appendix A with the Amendment and Response dated May 28, 2004), which is a published international application corresponding to the claimed invention. Example 2, at pages 19-26 of this PCT application, presents data demonstrating that relative to the unselected library, the potency (in terms of binding affinity for a substrate) of the selected population of non-peptide compounds (selected according to the claimed methods) was increased by approximately ***1000-fold*** (see in particular page 24, lines 30-32). It is, therefore, apparent that the actual results obtained through use of the

instantly claimed invention are not predicted from (i.e., are unexpected over) the teachings of the prior art.

Based on all of the foregoing, it is evident that the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit that this section 103(a) rejection is improper and request that it be reconsidered and withdrawn.

Rejection of Claims 1-7, 10-16 and 21-23 Under 35 U.S.C. §103 Over Lam et al. and Gallop et al., Further In View Of Benjamin et al.

The Examiner has rejected claims 1-7, 10-16 and 21-23 under 35 U.S.C. §103(a) as being unpatentable over Lam *et al.* (U.S. Patent 5,650,489) and Gallop *et al.* (Journal of Medicinal Chemistry. Vol. 37, Number 9, April 1994, pages 1233-1251), further in view of Benjamin *et al.* (US Patent 6,475,806 Bl). The Examiner relies on Lam *et al.* and Gallop *et al.* for the reasons stated above. The Examiner relies on Benjamin *et al.* for teaching "anchor libraries and identification of peptide sequences of peptide binding sequences. The anchor library taught by Benjamin et al has [the] same sequence as the instant specification peptide sequences. Benjamin et al teach that the anchor library is used to identify a peptide sequence that binds to the target."

Applicants disagree that the claimed invention would have been obvious to the ordinarily skilled artisan at the time it was made for at least the following reasons. First, the Lam *et al.* and the Gallop *et al.* references, cited by the Examiner, fail to teach or suggest forming a first library ***comprising a multiplicity of peptides***; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby ***generating a peptide motif***; forming a second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of

the at least one non-peptide compound that binds to the target, for the reasons set forth above with regard to the section 103(a) rejection of claims 1-3, 5-7, 10-16 and 21-23.

Furthermore, the secondary reference (Benjamin *et al.*), relied on by the Examiner does not make up for the above-stated deficiencies in the Lam *et al.* and the Gallop *et al.* references. Specifically, Benjamin *et al.* disclose creation of an anchor library and use of the anchor library to identify a peptide sequence that binds to the target but do not disclose forming a first library comprising a multiplicity of peptides; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby ***generating a peptide motif***; forming a second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library ***at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target***, as required by Applicants' claims. Moreover, as indicated above, the unexpected results achieved by use of the claimed invention demonstrate the non-obviousness of the invention.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw this section 103(a) rejection of claims 1-7, 10-16 and 21-23.

Rejection of Claims 1-7, 10-17 and 21-23 Under 35 U.S.C. §103 Over Lam et al. and Gallop et al., Further In View Of Stankova et al.

The Examiner has rejected claims 1-7, 10-17 and 21-23 under 35 U.S.C. §103(a) as being unpatentable over Lam *et al.* (U.S. Patent 5,650,489) and Gallop *et al.* (Journal of Medicinal Chemistry. Vol. 37, Number 9, April 1994, pages 1233-1251), further in view of Stankova *et al.* (Drug Development Research. Vol. 33, pages 146-156, 1994). The Examiner relies on Lam *et al.* and Gallop *et al.* for the reasons stated above. The Examiner relies on Stankova *et al.* for

teaching "the use of tandem mass spectroscopy for analysis of [the] structure of compounds identified fro[m] a library."

Applicants disagree that the claimed invention would have been obvious to the ordinarily skilled artisan at the time it was made for at least the following reasons. First, the Lam *et al.* and the Gallop *et al.* references, cited by the Examiner, fail to teach or suggest forming a first library ***comprising a multiplicity of peptides***; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby ***generating a peptide motif***; forming a second library comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, for the reasons set forth above with regard to the section 103(a) rejection of claims 1-3, 5-7, 10-16 and 21-23.

Furthermore, the secondary reference (Stankova et al.), relied on by the Examiner does not make up for the above-stated deficiencies in the Lam *et al.* and the Gallop *et al.* references. Specifically, Stankova *et al.* disclose screening non-peptide libraries by mass spectroscopy but do not disclose forming a first library comprising a multiplicity of peptides; selecting from the first library a family of peptides that bind to the target; determining the sequence or sequences of the family of peptides that bind to the target, thereby generating a peptide motif; forming a ***second library*** comprising a multiplicity of ***non-peptide compounds designed based on the peptide motif, wherein said multiplicity of non-peptide compounds are selected from the group consisting of peptide analogues, peptidomimetics and peptide derivatives***; selecting from the second library at least one non-peptide compound that binds to the target; and determining the structure or structures of the at least one non-peptide compound that binds to the target, as required by Applicants' claims. Moreover, as indicated above, the unexpected results achieved by use of the claimed invention demonstrate the non-obviousness of the invention.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw this section 103(a) rejection of claims 1-7, 10-17 and 21-23.

Provisional Rejection of Claims 1-7 and 10-23 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1-7 and 10-23 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of copending Application No. 10/610,927. In particular, the Examiner is of the opinion that

> [a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because both the reference and instant claimed methods are drawn to identifying non-peptide compounds, and the reference methods only differ by reciting 'biologically generated' first library which would include phage display library of instant claim 2; and further the reference method recites 'at least one peptide that binds to target' which is open to the instant claim method 'a family of peptides that bind to the target.'

While in no way admitting that claims 1-7 and 10-23 of the present application are obvious over claims 1-33 of co-pending Application No. 10/610,927, upon allowance of the '927 application Applicants will consider submitting a terminal disclaimer in that application in compliance with 37 C.F.R. 1.321(b) and (c), if appropriate, which will obviate this rejection.

CONCLUSION

In view of the above amendment, Applicants believe the pending claims are in condition for allowance.

Applicants believe that no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. PPI-012CNRCE from which the undersigned is authorized to draw.

Dated: September 8, 2005

Respectfully submitted,

By _____

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